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| (21) International Application Number: PCT/GB97/01201 (22) International Filing Date: 1 May 1997 (01.05.97) (30) Priority Data: 9609154.1 1 May 1996 (01.05.96) GB (71) Applicant (for all designated States except US): RHONE-POULENC CHEMICALS LIMITED [GB/GB]; Oak House, Reeds Crescent, Watford, Hertfordshire WD1 1QH (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): COE, Paul [GB/GB]; University of Birmingham, School of Chemistry, Edgbaston, Birmingham B15 2TT (GB). WARING, Tony [GB/GB]; University of Birmingham, School of Chemistry, Edgbaston, Birmingham B15 2TT (GB). MERCIER, Claude [GB/GB]; Rhône-Poulenc Chemicals, St. Andrews Road, Avonmouth, Bristol BS11 9YF (GB). (74) Agents: ELLIS-JONES, Patrick, George, Armine et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB). | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |
| (54) Title: PROCESS FOR THE PREPARATION OF FLUORO COMPOUNDS FROM THE CORRESPONDING AMINES (57) Abstract Compounds containing a primary amino group are converted into compounds containing a fluorine atom in place of the amino group by reaction of the amino compound with hydrogen fluoride and a nitrosating reagent under the influence of ultrasound or microwaves. | | |

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PROCESS FOR THE PREPARATION OF FLUORO COMPOUNDS
FROM THE CORRESPONDING AMINES

This invention relates to the preparation of fluoro compounds from amines by replacement of the amino group
5 by a fluorine atom.

It is known to produce fluoro compounds from corresponding amines, particularly aromatic amines, by conversion of the latter into a diazonium tetrafluoro-
borate salt which is then decomposed thermally to produce
10 the fluoro compound. It is also known to carry out the diazotization of aromatic amines in anhydrous hydrofluoric acid with subsequent heating to produce the corresponding fluoro compound. Neither of these methods is entirely satisfactory. The first involves isolation
15 of the tetrafluoroborate salt which is hazardous and time consuming. The latter method gives poor yields when substituted aromatic amines are used, especially if the substitution is in the ortho position. Also, the
reaction has to be carried out under pressure because
20 anhydrous hydrofluoric acid is volatile.

There have been a number of proposals of methods for the production of fluoro compounds which are said to give improved results. For example, European Specification
25 EP-A-0430434 (Imperial Chemical Industries plc.) describes a process for the preparation of fluoro aromatic and fluoro heteroaromatic compounds by reaction of corresponding aromatic or heteroaromatic amines with a

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of 100 w to 5kW.

This process is applicable to a wide variety of amino group containing compounds including more particularly aromatic and heteroaromatic primary amines and alpha-amino acids.

The invention may be, for example, applied to aromatic amino-compounds of the formula



where A is an unsubstituted or substituted aromatic or heteroaromatic radical and n is an integer, e.g. from 1 to 4. A may be for example a residue of benzene, naphthalene, diphenyl, acenaphthene, fluorene, or pyrene or a heteroaromatic compound such as pyridine or quinoline.

The invention may also be applied to α -amino acids such as alanine, valine, phenylalanine, isoleucine, tyrosine, and threonine, and to aralkylamines such as phenylethylamine.

Examples of suitable aromatic and heteroaromatic amines which may be subjected to the process of the present invention may be represented by the general formula:



where Ar is phenyl, α - or β -naphthyl, pyridyl, quinolyl, thienyl, or diphenyl, n is 0, 1, 2 or 3 and R is halogen, alkyl, hydroxy, alkoxy, COOH, CHO, alkoxycarbonyl, nitro, cyano, trifluoromethyl, carbamoyl, alkylcarbamoyl,

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nitrogen oxides.

In some cases improved yields are obtained by incorporating boron trifluoride etherate into the reaction mixture.

5 The amount of nitrosating reagent which is used in the process can be varied within wide limits. Preferably from 1.0 to 5.0, especially from 1.0 to 2.0 and more especially from 1.1 to 1.5, mole of nitrosating reagent is used per mole of primary amine.

10 The amount of hydrogen fluoride complex to primary amine can be carried within wide limits. Preferably 5 to 200, especially 10 to 50 and more especially 10 to 25, parts of liquid are used per part of primary amine.

 The reaction may be carried out at any temperature
15 in the range -20°C to $+150^{\circ}\text{C}$, but it is preferably carried out at 0 to 70°C , and especially at 0 to 50°C . The pressure is not critical and it is ordinarily convenient to carry out the reaction at ambient pressure.

 The ultrasound or microwaves may be provided using
20 commercially available sources, e.g. an ultrasonic cleaning bath or a microwave oven. The frequency of the ultrasound should be chosen to maximise absorption of energy by the reaction medium. Typically, the ultrasound should have an intensity of at least 20, preferably 50,
25 more preferably 100 and especially 200 W/cm^2 . Microwaves should have a frequency of 300 MHz to 3GHz and a power of 200 W to 5kW. (In some countries, the maximum frequency is fixed by law.)

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at 150-153°C @ atmospheric pressure. The distillation was complete in 45 minutes affording 1-fluoro-2,4,6-trimethylbenzene (2.1 g, 89.3%) as a colourless liquid.

The ^1H n.m.r. spectrum contained signals at δ_{H} (CDCl₃) 2.31, 2-CH₃ and 6-CH₃ (d, J=2.0 Hz, 6H); 2.32, 4-CH₃ (s, 3H); 6.88, 3-H and 5-H (d, J=7.0 Hz, 2H). The ^{19}F n.m.r. spectrum had a signal at δ_{F} (CDCl₃) 127.8, 1-F (s).

The mass spectrum produced a molecular ion at m/z 138 and the expected fragmentation pattern for 1-fluoro-2,4,6-trimethylbenzene at m/z 123, 109, 97, 91 and 83.

EXAMPLE 2

Diazotization of 2,6-dimethylaniline in Et₃N-3HF

The diazotization of 2,6-dimethylaniline (2.3 g, 0.02 mol) was performed under the same conditions as described for 2,4,6-trimethylaniline in Example 1. The reaction mixture turned yellow during the initial addition of sodium nitrite (2.0 g, 0.03 mol) and gradually turned red with the increased addition of sodium nitrite. Some tar was formed which was easily extracted with solvent. The work-up was identical to that described for 2,4,6-trimethylaniline. Diethyl ether (150 cm³) was used for the extraction of the organic layer from the aqueous washings. The organic extract was dried over magnesium sulphate.

Fractional distillation of the solvent formed an orange oil which was distilled at 141-143°C @ atmospheric pressure affording 1-fluoro-2,6-dimethylbenzene (2.0 g,

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liquid.

The ^{19}F n.m.r. spectrum had a signal at δ_{F} (CDCl_3) 121.9, 1-F (ddq, $J=8.5$ Hz, $J=10.5$ Hz and $J=2.2$ Hz). From the GC/MS the compound showed the expected molecular ion
5 at m/z 124 and the expected fragmentation for 1-fluoro-2,5-dimethylbenzene at m/z 109, 101, 96, 83 and 77.

EXAMPLE 4

Diazotization of 2,4-dimethylaniline in Et_3N -3HF

A similar approach was used for the diazotization
10 of 2,4-dimethylaniline as that described in Example 1. Addition of sodium nitrite (2.0 g, 0.03 mol) to 2,4-dimethylaniline (2.3 g, 0.02 mol), initially formed a yellow colour which eventually turned orange.

Diazotization became evident after 20 minutes when the
15 evolution of gas was vigorous. Very little undissolved sodium nitrite was detected at the end of the reaction.

Work-up as described in Example 1 for 2,4,6-trimethylaniline formed a brown oil on distillation of diethyl ether. Distillation of the oil at 143-144°C @
20 atmospheric pressure afforded 1-fluoro-2,4-dimethylbenzene (1.73 g, 74.6%) as a clear liquid.

The ^1H n.m.r. spectrum contained signals at δ_{H} (CDCl_3) 2.23, 2- CH_3 (d, $J=1.8$ Hz, 3H); 2.28, 4- CH_3 (s, 3H); 6.87, 6-H (t, $J=9.0$ Hz, 1H); 6.92, 5-H (ddd, $J=8.0$ Hz, $J=5.5$ Hz and $J=2.0$ Hz, 1H) and 6.97, 3-H (dm, $J=7.8$ Hz and $J=2.0$ Hz, 1H). The ^{19}F n.m.r. spectrum has a signal
25 at δ_{F} (CDCl_3) 124.2, 1-F (complex m).

The mass spectrum produced a molecular ion at m/z

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2,3-dimethylbenzene at m/z 109, 101, 96, 86, 83 and 77.

EXAMPLE 6

Diazotization of 3,4-dimethylaniline in Et₃N-3HF

3,4-Dimethylaniline (2.3 g, 0.02 mol) was added to
5 Et₃N-3HF in proportions (0.15 g) over a 40 minute period
at 0°C. Sodium nitrite (2.3 g, 0.03 mol) was added in
small quantities (100 mg) under the influence of
ultrasound. The slow addition of both substrates helped
to reduce the formation of tar. After the complete
10 addition of both substrates, the reaction vessel was
allowed to warm to room temperature and ultrasound was
applied for a further 10 minutes. The mixture was poured
into water (100 cm³). The organic layer was extracted
with diethyl ether (150 cm³ x 2) and dried over magnesium
15 sulphate.

Fractional distillation of the solvent afforded a
brown oil which was distilled at 138-139°C @ atmospheric
pressure affording 1-fluoro-3,4-dimethylbenzene (1.30 g,
56.1%) as a clear liquid. Attempts were made to extract
20 any material with a Soxhlet apparatus, but such measures
did not improve the isolated yield of the product. The
¹⁹F n.m.r. spectrum had a signal at δ_F (CDCl₃) 120.1, 1-F
(dddq, J=6.0 Hz, J=9.6 Hz, J=8.6 Hz and J=1.0 Hz). From
the GC/MS the compound showed the expected molecular ion
25 at m/z 124 and the expected fragmentation for 1-fluoro-
3,4-dimethylbenzene at m/z 109, 101, 97, 83 and 77.

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EXAMPLE 8Diazotization of 2-fluoroaniline in Et₃N-3HF

The diazotization of 2-fluoroaniline (2.3 g, 0.02 mol) was performed under the same conditions as those described for 4-fluoroaniline. Addition of sodium nitrite (2.0 g, 0.03 mol) caused the evolution of gas. The clear reaction mixture initially turned yellow and gradually darkened to a red colour. Some tar was formed during addition of sodium nitrite which was partially extracted with diethyl ether (30 cm³). The reaction mixture was poured into water (150 cm³) and extracted with diethyl ether (300 cm³). The combined ether extracts were dried over magnesium sulphate and fractional distillation of the solvent afforded a red oil.

Distillation of the oil at 88-90°C @ atmospheric pressure afforded 1,2-difluorobenzene (1.32 g, 55.9 %) as a clear colourless liquid.

The i.r. spectrum contained major peaks at ν_{\max} 3080 cm⁻¹ ($\nu_{\text{ArC-H}}$); 1620-1570 cm⁻¹ ($\nu_{\text{ArC=C}}$) and 1401-900 cm⁻¹ ($\nu_{\text{C-F}}$) and the ¹H n.m.r. spectrum showed signals at δ_{H} (CDCl₃) 7.05-7.25 (complex m). The ¹⁹F n.m.r. spectrum had a signal at δ_{F} (CDCl₃) 138.9, 1-F, 2-F (ddd, J=9.0 Hz, J=9.0 Hz and J=5.5 Hz).

The mass spectrum produced a molecular ion at m/z 114 and the expected fragmentation pattern for 1,2-difluorobenzene at m/z 94, 88, 81, 75, 70 and 63.

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The mass spectrum produced a molecular ion at m/z 96 and the expected fragmentation pattern for fluorobenzene at m/z 92, 75, 70 and 63.

EXAMPLE 10

5 Preparation of 1,2-difluorobenzene
in HF/THF with ultrasound

An FEP container was initially cooled to -78°C with acetone/Drikold and carefully charged with HF/THF (4:1). 2-Fluoroaniline (5.0 g, 0.05 mol) was added to the HF/THF
10 mixture under vigorous stirring and allowed to warm to -10°C . When the desired temperature was reached the container was transferred to an ultrasonic bath containing an ice-salt water mixture. The container was fitted with a Drikold condenser adapted with a
15 polypropylene filter funnel.

Sodium nitrite (4.95 g, 0.07 mol) was added over 35 minutes under the influence of ultrasound. During the addition an exothermic reaction occurred with the evolution of a brown gas. The ultrasound was applied for
20 a further 1 hour after the complete addition of sodium nitrite at room temperature. The mixture was further heated for 1 hour at 45°C under the influence of ultrasound. Dediazonation was complete after 1 hour. The mixture was poured onto iced water (150 cm^3). The
25 organic constituents were extracted with dichloromethane ($200\text{ cm}^3 \times 2$). The extracts were finally washed with water (100 cm^3), stirred with sodium fluoride (2.5 g) and dried with magnesium sulphate for 12 hours.

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atmospheric pressure afforded to clear liquid of 1,4-difluorobenzene at 87-88°C (3.16 g, 62.0 %). Without ultrasound, the yield is only 40%.

EXAMPLES 12 AND 13

- 5 The addition of BF₃-etherate complex has helped to improve the yield of isolated 1,2-difluorobenzene and 1,4-difluorobenzene as shown below.

| | <u>Substrate</u> | <u>Product</u> | <u>Yield %</u> | <u>Conditions</u> |
|----|------------------|---------------------|----------------|--------------------------------------------------------------------|
| 10 | 2-fluoroaniline | 1,2-difluorobenzene | 60 | NaNO ₂ , BF ₃ etherate with ultrasound |
| 15 | 4-fluoroaniline | 1,4-difluorobenzene | 68 | NaNO ₂ , BF ₃ etherate with ultrasound |

- 20 The procedures used for these reactions are similar to Examples 10 and 11. 5 cm³ of the BF₃ etherate complex were used.

EXAMPLES 14, 15 and 16

- 25 Proceeding as in Example 1, the following α -amino acids were converted into the corresponding α -fluoroacids in the stated yields:

| | | |
|------------|------------------|-----|
| Example 14 | β -alanine | 50% |
| Example 15 | DL-Valine | 75% |
| Example 16 | L-phenylalanine | 70% |

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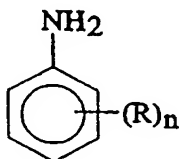
CLAIMS

1. Process for converting a compound containing a primary amino group into a compound containing a fluorine atom in place of said amino group which comprises contacting said amino-group-containing compound with hydrogen fluoride, or with a complex thereof with a base, and a nitrosating reagent at a temperature in the range -20° to $+150^{\circ}\text{C}$ while subjecting the reagents to the action of ultrasound having a frequency of 10 to 100 kHz and an intensity of at least 20 Watts/cm² or to the action of microwaves having a frequency of 300 MHz to 3GHz and an intensity between 100W and 5kW.

2. Process according to claim 1 wherein the amino-group-containing compound is an aromatic or heteroaromatic primary amine or an α -amino-acid.

3. Process according to claim 1 wherein the amino-group-containing compound is a compound of formula

20



where n is 0, 1, 2 or 3 and the radicals R, which may be the same or different when n is 2 or 3, are each halogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms, carboxy, alkoxycarbonyl with 1 to 4 carbon atoms in the alkoxy, nitro, cyano or trifluoromethyl.

4. Process according to any one of claim 1 to 3

INTERNATIONAL SEARCH REPORT

National Application No
PCT/GB 97/01201

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| A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07B39/00 C07C17/093 C07C25/13 | | |
| According to International Patent Classification (IPC) or to both national classification and IPC | | |
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07B C07C | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched | | |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used) | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | CHEMICAL ABSTRACTS, vol. 110, no. 3, 16 January 1989 Columbus, Ohio, US; abstract no. 023510, YONEDA N ET AL: "Preparation of aromatic fluorides by photochemical diazotization and decomposition of aromatic amines" XP002034108 see abstract & JP 63 188 631 A (MITSUBISHI KASEI CORP.;JAPAN) 4 August 1988 --- | 1 |
| A | EP 0 467 742 A (RHONE POULENC CHIMIE) 22 January 1992 see claims --- <div style="text-align: center;">-/-</div> | 1 |
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| Date of the actual completion of the international search <div style="text-align: center;">1 July 1997</div> | | Date of mailing of the international search report <div style="text-align: center;">1 0. 07. 97</div> |
| Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016 | | Authorized officer <div style="text-align: center;">Bonnevalle, E</div> |

INTERNATIONAL SEARCH REPORT

Information on patent family members

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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| EP 0467742 A | 22-01-92 | FR 2664588 A | 17-01-92 |
| | | FR 2664589 A | 17-01-92 |
| | | JP 4244049 A | 01-09-92 |
| | | US 5354439 A | 11-10-94 |
| US 3481850 A | 02-12-69 | NONE | |
| CH 141750 A | | NONE | |

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